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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/714,409	11/14/2000	Leisa Johnson	ONYX1033ord	5051

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Gregory Giotta
ONYX Pharmaceuticals Inc
3031 Research Drive
Richmond, CA 94806

EXAMINER	
NGUYEN, DAVE TRONG	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 09/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/714,409	JOHNSON ET AL.	
	Examiner	Art Unit	
	Dave T Nguyen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,5,7,8,11,12 and 14-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7,8,11,12 and 14-16* is/are rejected.

7)☐ Claim(s) *4, 5* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 22, 2004 has been entered.

Claim 7 has been amended by the amendment filed on June 22, 2004.

The examiner acknowledges that claims 15 and 16 were indicated incorrectly as being canceled by the amendment dated September 17, 2003. However, such is not a case. Thus, this office action will address the claimed inventions as claimed in claims 15 and 16.

Claims 1, 4, 5, 7, 8, 11, 12, and 14-16, to which the following grounds of rejection remain and/or are applicable, are pending.

After a close review of the claimed invention and the as-filed application, which teaches the essential requirement of having an E2F responsive transcriptional regulatory sequence as a promoter, a new ground of rejection has been set forth for claims 1, 8, 15, and 16.

Claim Rejections - 35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full,

clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 8, 15, 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

I) An adenoviral vector comprising an E2F responsive transcriptional regulatory sequence that promotes the expression of an early adenoviral gene, and a mutation in the E1A region of said adenoviral vector, which mutation causes a loss of RB binding to the protein encoded by the E1a region, does not reasonably provide enablement for an adenoviral vector comprising an E2F responsive transcriptional regulatory site that is not necessarily a promoter and yet control the expression of an early adenoviral gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The as-filed application only teaches and discloses the make and use of an adenoviral vector comprising an E2F responsive promoter operably linked to an early adenoviral gene. For example, the application discloses on page 19 that an E2F responsive promoter, which contains E2F binding sites, is used to substitute for the E4 basis promoter for tumor specificity. Moreover, page 23 of the specification states:

What is intended in describing the invention is that in the place of the endogenous promoters, the E2F responsive promoter functions to drive the E1a and/or E4 genes to kill tumor cells.

The specification does not teach and disclose any other E2F responsive transcriptional regulatory site that is not necessarily a promoter and yet control the expression of an early adenoviral gene so as to use such adenoviral vector within applicant's intended usage of the vector, *e.g.,* tumor specific adenoviral vector in cancer treatment.

As such, it would require an undue experimentation for a skilled artisan to make and use any other E2F responsive transcriptional regulatory site that is not necessarily a promoter and yet control the expression of an early adenoviral gene, particularly on the basis of applicant's disclosure.

Note that should the claimed be amended to recite such enabling embodiments, claims 4 and 11 should be canceled so as to avoid duplication.

Claim 16 is rejected under 35 U.S.C. 112, first paragraph because the specification is enabling only for claims limited to:

A method for killing cancer cells, comprising the steps of directly injecting to a cell population comprising cancer cells and normal cells the adenoviral vector of I), thereby killing said cancer cells in the presence of the normal cells.

Claim 16 is readable on an *in vivo* method of propagating any replication

competent viral vector in cancer cells without little or no killing of non-neoplastic cells in any cancer cells bearing animal so as to produce a therapeutically relevant effect. The state of the art exemplified by Russell (European Journal of Cancer, Vol. 30A, 8:1165-1171, August 1994) states that "cell-specific utilisation of the albumin (liver specific) and immunoglobulin (B-cell specific) promoters has been demonstrated within non-replicating adenovirus genomes but cell specificity was partially lost after replication of the viral DNA", and that the stoichiometry and kinetic of gene regulation by cellular transcription factors must be known for engineering the promoters of replicating vectors for tissue-specific, transformation-dependent expression (p. 1168, column 2). In addition, Miller *et al.* (Human Gene Therapy, Vol. 8, pp. 803-815, 1997) teaches (page 807, column 1) that problems with vectors for tissue specific replication include:

- "Interference of vector sequences with regulatory sequences, particularly where the vector is derived from a virus";
- "Interference from sequences after vector integration, *i.e.,* positional effects";
- "Non specific effects on host transcription".

More specifically, Miller *et al.* states:

"It was found that PKA activators such as aminophylline enhanced expression of cytokine genes driven by the tyrosinase promoter in melanoma but not fibroblast cell lines (Miller *et al.,* 1995). Unfortunately, this effect could not be duplicated *in vivo* (possibly the activity of the tyrosinase promoter differs between a there-dimensional tumor mass *in vivo* and a two-dimensional monolayer *in vitro*".

In addition, Vile *et al.* (Molecular Medicine Today, Vol. 4, 2:84-92, 1998, p. 90, column 1) teach that "the relevant locus control regions/enhancer/silencer/promoter sequences that control expression can be distributed over many kbp and within chromatin domains that are difficult to reproduce within the context of the vector systems", and that "the combinations of these elements in certain configurations of these elements might be successful in the context of one vector (such as plasmid DNA), but their specificity might be altered or lost in a different context (such as retrovirus or adenovirus)". As to the problem of adenoviral leakiness, Gomez-Navarro *et al.* (European J. of Cancer, Vol. 35, 6:867-885, 1999) states that "it has been reported that certain tumour-specific regulatory elements lose their specificity in the context of an adenoviral vector" (p. 878, column 2, last par.), and that "major problems remain to be solved before these approaches can become effective and common place strategies for cancer (p. 881, column 1, last par.), Moreover, Yanez (Gene Therapy, 5:149-159, 1998) states:

> While Gene targeting has been achieved both in human cell lines and in nontransformed, primary human cells, its low efficiency has been a major limitation to its therapeutic potential. Gene therapy by in vivo gene targeting is therefore impractical without dramatic improvements in targeting efficiency.

Thus, it is not apparent how any of the disclosed tissue-specific vectors when used in the context of an application of an E2F responsive promoter, let alone other unspecified E2F responsive regulatory sites, is distributed and/or targeted only in a desired *in vivo* cancer cells for replication and subsequent expression of a heterologous

gene, thereby generating any therapeutically useful effect, particularly on the basis of applicant's disclosure and given the doubts expressed by the art of record.

With regard to claims directed to tissue-specific replication-conditional adenoviral vectors (which is a preferred species of the claimed invention), the adenoviral genes, E1b, E2, E1A, and E4 (all essential for replication of adenovirus vectors) encode proteins whose functions are dissimilar with each other. Each of these genes or regions requires a certain level of expression to support adenoviral replication. Note also cited prior art of Hallenbeck (WO 96/17053) teaches that the expression levels of adenoviral genes essential for replication, *e.g.,* E1 and E4, must be carefully regulated in order to averse toxicity effect of the adenoviral genes upon the cells or tissues transformed with adenovirus vectors. Since it is known in the art (Russell, Vile *et al.*) that tissue-specific cellular promoters activate constitutive expression of a transgene in a target tissue thereby leading to an uncontrollable replication of the introduced replication competent adenovirus vectors, it is not apparent how the expression levels of E4 gene, for example, are regulated *in vivo* from the claimed adenoviral vectors in order to avoid the toxicity to normal cells *in vivo* (due to leakage of the adenovirus replicons to nearby tissues and cells) before a therapeutically useful effect can be generated. There is no discussion in the specification of expression levels necessary to achieve appropriate expression for specific replication in a target tissue or cells *in vivo* so that toxicity would not occur to an *in vivo* subject before a therapeutically useful effect can be generated.

More specifically as to claimed methods of distributing a polynucleotide in a tissue *in vivo* using any of the claimed vectors, the claims encompass gene-targeted

therapy in any subject including a human. The application contemplates that claimed cancer gene therapy method using any known routes of administration would deliver and express the claimed viral vectors in any target cancer site *in vivo* in a sufficient amount required for its conditional replications so as to generate a therapeutically killing effect only in those cancer cells, with little or no killing of non-neoplastic cells. However, the state of the art exemplified by Anderson (Nature, Vol. 392, pp. 25-30, April 1998) indicates that major considerations for any gene transfer or gene therapy protocol involve issues including amount of DNA constructs to be administered, what amount is considered to be therapeutically effective for all of the claimed nucleic acid molecules, the route and time course of administration, the sites of administration, successful uptake of the claimed DNA at the target site, expression of the DNA at the target site in amounts of effecting the claimed methods. In addition, Anderson teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (page 30, column 1, last paragraph). Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack a basis understanding of how vectors should be constructed, what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph).

More specifically as to the state of the art of cancer gene therapy, Mastrangelo *et al.* (Seminars in Oncology, Vol. 23, No. 1:4-21, 1996) teaches:

- "c[C]ritical to the success of gene therapy is the efficient gene transfer (transfixing) of a functional gene to the target cell. This has proven a major stumbling block, particularly for in vivo gene transfer" (page 10, column 1, first paragraph); and

- "to date the major successes with gene therapy for cancer have been limited to *in vitro* systems where tumor cells with well defined genetic defects are easily targeted" (page 13, column 2, first paragraph).

Meng *et al.* (Gene Therapy of Cancer, Chapter I, pp. 3-20, 1999) teach that factors including specific genes used for a treatment, gene delivery vectors, routes of administration, and gene expression are all critical for the success of a gene therapy method (pages 4-6). For example, Meng *et al.* teach that "it is difficult to prepare sufficiently high titers of retroviruses for *in vivo* gene therapy", that "the most significant drawback to adenoviruses, however, is that they elicit a strong host immune response", and that "although it may seem intuitive that a heightened immune response may be good in cancer gene therapy, it is less desirable on a practical scale because the immune response helps to eliminate the vector and to decrease the expression of the transduced gene" (p. 4, column 2, last paragraph). Meng *et al.* further teach that "although animal studies have suggested low toxicity and excellent efficacy, these investigations have been limited by the use of immuno-deficient mice" (p. 6, column 1).

In fact, Meng *et al.* teach that other than intratumor injection, delivery of virally expressed genes by intravascular or intracavitary injections also presents barriers to the delivery of the target genes (p. 6, column 1). For example, Meng *et al.* state:

> "In intravascular administration, instillation into a peripheral vein dilutes the vehicle, so only a small portion may ultimately reach the tumor. Intravascular administration also elicits a powerful immune response. Tropism for organs such as the liver, for example by adenovirus, can be a disadvantage if delivery is intended elsewhere or may be advantageous if the liver is the target. Even with regional intravascular administration, the virus must traverse the endothelial wall and travel against pressures within an expanding tumor mass." (page 6, column 1).

While transient gene expression has been observed in cells *in vivo* at the time of filing using routes of administration other than intratumoral administration, it is not apparent how a randomly transient gene expression in a tumor bearing animal is reasonably correlated to any meaningful or sufficient amounts of the claimed viral vectors inside only target cancer cells so as to produce only targeted killing effects in the cancer cells, particularly given the doubts expressed in the art of record. The skilled artisan then next turns for evidence from applicant 's disclosure in order to practice the claimed methods. However, the as-filed specification does not provide sufficient guidance and/or evidence to overcome and/or resolve the outstanding issues and barriers expressed by the art of record with respect to cancer targeted gene therapy of using any viral vector. As such, the specification fails to teach one of skill in the art how to overcome the unpredictability for vector targeting such that efficient gene transfer is achieved by <u>any</u> other mode of delivery other than intratumoral administration.

In view of the reasons set forth above, the nature of the invention, the unpredictability of gene therapy, and the breadth of the claims, it is not apparent as to how one skilled in the art practices the full scope of the claimed invention without undue experimentation.

Applicant response in the response dated 9/17/03 has been considered by the examiner but is not found persuasive. Applicant mainly asserts that since none of the cited prior art employs specifically the claimed adenoviral vector at issue, the rejection is not correct. However, the stated rejection pertains to unpredictably factor of using adenoviral vectors *in vivo* for therapeutic efficacies such as efficiency, expression level, and routes of administration of such vectors in achieving a cancer treatment. A reasonable person skilled in the art would have recognized that there are numerous problems associated with targeted cancer gene therapy at the time the invention was made, and would have expected, that the claimed invention, in so far as it pertains to the use of an adenoviral vector, regardless of its specific structure, is not enabling to its full breadth at the time the invention was made, particularly on the basis of the reasons as set forth in the stated rejection and art of record. Given that no evidentiary support has been given in the as-filed application to rebut the doubts expressed and a reasonable conclusion of the unpredictable nature of the claimed invention as broadly claimed, the stated rejection remains proper, and thus, is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7, 8, 11, 12, 14-16 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 is indefinite in the recitation of "substantially" because it is not apparent what are exactly considered to be within the metes and bounds of the "substantially facilitate viral replication". The examiner also notes that claim 7 claims an adenoviral vector, and yet the phrase "substantially facilitate viral replication" does not appear to refer specifically to adenoviral replication. Clarification is requested in regard to "viral replication". Further, the claim is written in such as way that is not apparent as to what is exactly an entity that comprises Sp1, ATF, NF1 and NFIII/Oct-1, nor is apparent as to what Sp1, ATF, NF1 and NFIII/Oct-1 supposes to mean if the term "binding site" is not inserted immediately thereafter. Should applicant intend to claim regulatory sites comprising Sp1, ATF, NF1 and NFIII/Oct-1 binding sites, wherein the sites facilitates adenoviral replication, the claim should be amended to reflect such so as to obviate the rejection.

Claim 8, and claims dependent there from, *e.g.,* claims 11, 12, 14-16, are indefinite in the recitation of "said viral gene" since the term does not contain a proper antecedent basis. A change to – said early adenoviral gene -- is suggested.

In claim 15, the term "said transcriptional regulatory sequence" lacks an antecedent basis. The base claims do not recite a "transcriptional regulatory sequence" as referred by

claim 15. In addition, the term "human E2F-1" is not clear since it is not apparent as to what exactly the term refers to. The term is incomplete in the absence of the word "promoter" inserted immediately thereafter.

The prior art rejections have been withdrawn by the examiner because of the reasons as set forth in Applicant's response (dated June 22, 2004), particularly pages 5 and 6. In other words, the prior art teaches either a) a targeted Adenoviral vector consisting essentially a mutated adenoviral E1A region can be used to target neoplastic cells for replication and killing of the cells, whereby replication of the vector is impaired in normal cells as the result of the inability of RB to bind to the mutated E1A protein, or b) a targeted adenoviral vector comprising a E2F1 promoter operably linked to a wild typed E1A coding region, whereby expression of the E1A and subsequent replication of the vector only occur in neoplastic cells While there is a general teaching or suggestion from the prior art of record to use a E2F1 promoter in an adenoviral vector used in a tumor treatment, there is no teaching or suggestion specifically from any of the prior art of record to employ a) and b) together. Given that one of ordinary skill in the art would have expected that the either the adenoviral vector of a) or b) is sufficient for targeting only neoplastic cells for an cancer effect and leaving alone the normal cells, and since both are designed for the same goal, the claimed invention as presently pending is free of the prior art of record.

Claims 4, 5 are objected as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **571-272-0731**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Amy Nelson*, may be reached at **571-272-0804.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center number, which is **703-872-9306.**

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Primary Examiner
Art Unit: 1632

DAVE T. NGUYEN
PRIMARY EXAMINER